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Addendum for Endrin

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ADDENDUM FOR ENDRIN

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OFFICE OF WATER REGULATIONS
AND STANDARDS

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PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under contract no. 68-C8-0004.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
CBI	Confidential business information
CRAVE	Carcinogen Risk Assessment Verification Endeavor
EEG	Electroencephalogram
MTD	Maximum tolerated dose
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PEL	Permissible exposure limit
ppm	Parts per million
RFD	Reference dose
TLV	Threshold limit value
TWA	Time-weighted average

INTRODUCTION

Under Section 304(a)(1) of the Clean Water Act of 1977 as amended in 1987, the U.S. EPA is required to publish criteria for water quality accurately reflecting the latest scientific knowledge regarding the effects on health and welfare that may occur from the presence of pollutants in any body of water, including groundwater. In accordance with the 1977 act, Ambient Water Quality Criteria Documents (AWQCDs) were developed in 1980 for 65 toxic pollutants or classes of pollutants listed under Section 307(a)(1).

These addenda are intended to serve as an update of the original AWQCDs. The addenda provide the Agency with the latest scientific assessments of potential health hazards associated with these pollutants and serve as guidelines for modifying the current (1980) AWQCDs.

The human health criteria in these addenda are based on Agency verified risk assessment values when available. These values consist of reference doses (RfD) for those chemicals believed to be systemic toxicants (i.e., do not induce cancer) and cancer risk factors for those thought likely to cause cancer in humans. The verification process consists of a review and consensus of risk assessment values provided by an Agency workgroup consisting of scientists from each of the major Agency offices. Assessments for noncarcinogens are verified by the RfD workgroup and those for carcinogens are verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) workgroup. If such values are not available, the criteria are based on the most recent Agency health assessment. In the absence of any appropriate Agency value, RfD values or cancer risk factors are derived by current Agency methods if adequate new data are available, and criteria are recommended based on the proposed RfD or risk factor.

The RFD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RFD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$RFD = \frac{NOAEL \text{ or } LOAEL}{UF(s) \times UF}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RFDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen; Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); Group D - Not Classifiable as to

Human Carcinogenicity (Inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multistage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQCD on endrin, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1987 to 1988). New key studies have been evaluated.

REVIEW OF NEW DATA

Toxicologic/Carcinogenic Effects

In a study by Nelson et al. (1956), not cited in U.S. EPA (1980), groups of 10 Sprague-Dawley rats (5/sex) were fed diets containing endrin at concentrations of 0, 1, 5, 25, 50 and 100 ppm for ≤ 16 weeks. Rats exposed to 25, 50 or 100 ppm had convulsions. Within 2 weeks, mortality in the 100 ppm group was 100%. After 16 weeks, some mortality occurred in all groups of males, but only in females exposed to ≥ 25 ppm. A dose-dependent increase in alkaline phosphatase was also observed among survivors. In all exposed groups, body weights decreased after 16 weeks compared with controls.

In another study not cited in U.S. EPA (1980), Speck and Maaske (1958) administered endrin orally to groups of male Sprague-Dawley rats at 0, 0.8, 1.7 or 3.5 mg/kg/day in peanut oil 5 days/week from 1 week to 7 months. Four of 30 animals died after 1 week of treatment at the highest dose. Surviving animals from this group exhibited irritability, increased ventilation frequency and a predisposition to convulsions following auditory stimulation. Minimal EEG changes were seen in chronic groups. After 3 months of exposure, livers of the highest dose animals appeared spotty, with zones of basophilic cells around the central and portal veins. Moreover, a significant reduction in plasma specific gravity was noted in this group after 3 months of endrin exposure; this effect was reversed when exposure ceased.

Kavlock et al. (1981) treated pregnant CD rats with endrin dissolved in corn oil at 0.075, 0.150, 0.300 or 0.450 mg/kg/day by gavage on days 7-20 of gestation. Rats necropsied on gestation day 21 showed a marked reduction in maternal body weight at 0.300 and 0.450 mg/kg/day. No effects were seen on relative liver weights, fetal implants, mortality or fetal body weights. In the same study, CD-1 mice were treated with 0.5, 1.0, 1.5 or 2.0 mg/kg/day

on gestation days 7-17. Maternal mortality increased in a dose-related manner at 1.5 and 2.0 mg/kg/day. In addition, there was a dose-related reduction in maternal body weight gain at ≥ 1.0 mg/kg/day and a dose-related increase in relative liver weight in all treated groups. A dose-related decrease in fetal body weights and delayed skeletal development were also seen at ≥ 1.0 mg/kg/day.

Walker and Phillips (1987) studied the effect of subchronic doses of endrin on the ultrastructure of peripheral nerve fibers in mice. Ten-week-old male CD-1 Swiss mice averaging 34 g in weight were given daily intraperitoneal injections of endrin in sesame oil at doses increasing from 1.5 mg/kg/day on days 0-3, to 2.0 mg/kg/day on days 4-11 to 4.0 mg/kg/day on days 12-19. Groups of animals (four experimental and two control) were sacrificed after 4, 7, 14 and 20 days of exposure and 14 and 92 days after the last injection. The animals were perfused with glutaraldehyde and the sciatic nerve was removed and processed for electron microscopy. During the exposure period, endrin-treated animals showed signs of hyperactivity and appeared hypersensitive to external stimuli compared with controls; however, 14 days after the treatment was terminated the general behavior of the treated animals appeared similar to that of vehicle control animals. During the 20-day exposure, 23% of the animals died. There was no mortality after exposure ceased. Myelinated fibers and associated Schwann cells of endrin treated mice did not appear different from control fibers; however, marked ultrastructural changes were present in the unmyelinated fibers and associated Schwann cells of exposed animals. Unmyelinated axons were swollen, there was dissolution of microtubules and neurofilaments and most axons contained little structured material. Although common early in the treatment, swelling decreased progressively during the exposure period and

recovery. The results of this study (Walker and Phillips, 1987) do not clarify why the effect was seen only in unmyelinated fibers. An important question is whether the affected axons can still conduct nerve impulses.

The verified oral RfD for endrin is derived from a CBI study (U.S. EPA, 1987a). In this 2-year study, beagle dogs (7/sex/group) received diets containing 0, 0.1, 0.5, 1.0, 2.0 and 4.0 ppm endrin for a period of >2 years. Two groups of dogs (2/sex/group) were sacrificed at 6 and 12 months. The parameters monitored were growth, food consumption, behavior, serum and urine chemistry, organ weights and histopathology of all major organs. Animals treated with 2 and 4 ppm dose levels had convulsions, a slight increase in relative liver weights and mild histopathological changes in liver cells. Because effects were observed with a 2 ppm dose (0.05 mg/kg/day) of endrin, this value constitutes the LOAEL. Since no adverse effects were observed in dogs receiving diets containing 1 ppm endrin (0.025 mg/kg/day), this value was considered the NOEL.

The potential carcinogenic effects of endrin have been evaluated in Carworth Farm rats (Treon et al., 1955), Osborne-Mendel rats (Deichmann et al., 1970; NCI, 1979), C57B1/CJ mice (Witherup et al., 1970), C3D2F1/J mice (Witherup et al., 1970) and B6C3F1 mice (NCI, 1979). In all these studies the results were negative (U.S. EPA, 1987a,b). In addition, Treon et al. (1955) observed no increase in tumor incidence in dogs exposed at the MTD (0.15-0.21 mg/kg/day) for ≤ 18.7 months. However, the length of this study was insufficient to provide for the expected latency period in dogs. Reuber (1978) reported positive carcinogenic effects of endrin observed in an FDA bioassay. Male and female Osborne-Mendel rats were administered endrin in the diet at concentrations of 0.1, 1, 5, 10 or 25 ppm, and the total number of malignant tumors increased in all exposed groups. No dose-response

effect was apparent; the greatest number of tumors occurred in the 0.1 ppm group. In addition, Reuber (1979) independently reevaluated the NCI (1979) study as well as the FDA study and concluded that the results were positive. The conclusion is considered questionable, since the criteria appear to differ from those of other investigators (U.S. EPA, 1987a,b). Using the criteria in the U.S. EPA (1986) guidelines for classification of carcinogens, endrin is most appropriately classified in Group D, not classifiable as to human carcinogenicity, meaning there is inadequate animal and human evidence (U.S. EPA, 1988b). This classification is based on the nonpositive but suggestive results in some of the animal studies.

Bioconcentration Factor (BCF)

In the 1980 AWQCD (U.S. EPA, 1980), the mean BCF value for endrin, after normalization to 1% lipids, was 1324 and the weighted average BCF was 3970. In 1981, the mean BCF value was changed to 1834 and the weighted average BCF was changed to 5500 (Stephan, 1981).

QUANTIFICATION OF EFFECTS

The 1980 AWQCD calculated a criterion for endrin of 2.5 $\mu\text{g}/\text{l}$ for the ingestion of water and fish and shellfish (U.S. EPA, 1980). In calculating this value, a BCF of 3970 was used. However, the 1980 AWQCD recommended a criterion of 1 $\mu\text{g}/\text{l}$ (comparable to the maximum allowable concentration for endrin proposed by the Public Health Service for drinking water). U.S. EPA (1980) warns that a criterion of 1 $\mu\text{g}/\text{l}$ may not be sufficient to protect a special high risk group (i.e., pregnant women who consume a single dose of endrin-contaminated fish). Given a BCF of 3970, a 250 g portion of fish would contain ~1.0 mg of endrin (0.02 mg/kg for a 50 kg female). This represented a highly questionable margin of safety of only 75 over a NOEL of 1.5 mg/kg for teratogenicity in hamsters (Chernoff et al., 1979). U.S. EPA (1980) indicated that teratologic effects are more likely to occur with acute exposures at critical times during gestation.

The value of 2.5 $\mu\text{g}/\text{l}$ was derived from two long-term studies conducted by Treon et al. (1955) in rats and dogs. Rats were fed 0, 1, 5, 25, 50 or 100 ppm endrin for 2 years. Increased mortality and general toxicity developed in the two higher dose groups. Relative liver weights were increased in males at 5 and 25 ppm, whereas no effects were seen in rats fed 1 ppm. Doses estimated by the U.S. EPA (1980) using a food factor of 0.1 were 0.5 mg/kg/day at 5 ppm and 0.1 mg/kg/day at 1 ppm. Dogs were given a 1-50 ppm endrin diet for ≤ 18 months. All dogs fed 10-50 ppm died; >50% of those fed 5-8 ppm died, growth was affected at 4 ppm and increased relative kidney and heart weight was seen at 3 ppm (0.12-0.25 mg/kg/day). No adverse effects were seen at the 1 ppm level (0.045-0.120 mg/kg/day). Dosages were

calculated by the investigators. An uncertainty factor of 100 was applied to the dog NOEL of 0.1 mg/kg/day, resulting in an ADI of 1 μ g/kg/day or 70 μ g/day for a 70 kg man.

Although the study by Treon et al. (1955) was extensive, the unpublished CBI study was considered the most appropriate basis for deriving an oral RfD (U.S. EPA, 1987a, 1989). In this 2-year study (see previous section), no adverse effects were seen in dogs receiving 1 ppm endrin (0.025 mg/kg/day, NOEL), and mild hepatic lesions were seen in dogs receiving 2 ppm (0.05 mg/kg/day, LOAEL). This LOAEL is similar to the NOEL in the dog study of Treon et al. (1955). Since the CBI study provides data for the most sensitive species exposed for the longest period, is well-designed and conducted, and monitored all important toxicologic endpoints, the NOEL from the CBI study was chosen as the basis for the verified RfD (U.S. EPA, 1989). Applying an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for sensitive human subpopulations) to the NOEL of 0.025 mg/kg/day resulted in an oral RfD of 0.00025 mg/kg/day (U.S. EPA, 1987a, 1989), which was rounded to 0.0003 mg/kg/day and verified (U.S. EPA, 1989).

The verified oral RfD is the best basis for ambient water quality criteria. Stephan (1981) recommended a revised mean BCF value of 1834 and a weighted average BCF of 5500. Using the unrounded RfD value of 0.00025 mg/kg/day, and assuming an average human water consumption of 2 L/day, fish and shellfish consumption of 6.5 g/day, a 70 kg adult, and using a BCF of 5500 (Stephan, 1981) for endrin, a criterion for consumption of water and fish and shellfish of 0.46 μ g/L is calculated. The criterion for consumption of fish and shellfish alone, using the same assumptions as above, is 0.49 μ g/L. Using the revised BCF of 5500 and the verified RfD, the margin of safety for teratogenic effects would be 107 as compared with the previously calculated value of 75.

EXISTING STANDARDS AND CRITERIA

As described in the previous section, the chronic RfD for oral exposure was verified on April 20, 1988, and is 0.0003 mg/kg/day based on the NOEL of 0.025 mg/kg/day for histological appearance of major organs, behavior, serum and urine chemistry, growth and food consumption in dogs. An uncertainty factor of 100 was used (U.S. EPA, 1989). HAs for endrin (U.S. EPA, 1987a,b) are as follows: 1-day (10 kg child), 0.05 mg/l; 10-day (10 kg child), 0.02 mg/l; longer-term (10 kg child), 0.003 mg/l; longer-term HA and DWEL (70 kg adult), 0.009 mg/l. Values for a child assume 1 l/day water consumption; for adults, 2 l/day water consumption. The longer-term HA and the DWEL are based on the NOEL of 0.025 mg/kg/day from the chronic oral study in dogs (see previous section).

Endrin is classified in Group D, not classifiable as to human carcinogenicity, meaning there is inadequate animal and human evidence (U.S. EPA, 1989). This classification was verified on October 19, 1988.

The OSHA (1985) PEL and the ACGIH (1987) TLV-TWA for endrin is 0.1 mg/m³; both agencies note that endrin can be absorbed through the skin.

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